

Complete Summary

GUIDELINE TITLE

Radiopharmaceuticals for the palliation of painful bone metastases.

BIBLIOGRAPHIC SOURCE(S)

Therapeutic Radiopharmaceutical Guidelines Group. Radiopharmaceuticals for the palliation of painful bone metastases [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Jun 15. 36 p. (Practice guideline report; no. 14-1). [74 references]

COMPLETE SUMMARY CONTENT

SCOPE
 METHODOLOGY - including Rating Scheme and Cost Analysis
 RECOMMENDATIONS
 EVIDENCE SUPPORTING THE RECOMMENDATIONS
 BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
 QUALIFYING STATEMENTS
 IMPLEMENTATION OF THE GUIDELINE
 INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT
 CATEGORIES
 IDENTIFYING INFORMATION AND AVAILABILITY

SCOPE

DISEASE/CONDITION(S)

Bone metastases

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
 Treatment

CLINICAL SPECIALTY

Internal Medicine
 Nuclear Medicine
 Oncology
 Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the role of radiopharmaceuticals in the palliation of metastatic bone pain

TARGET POPULATION

Adult cancer patients with uncomplicated, multifocal painful bone metastases above and below the diaphragm whose pain is not controlled with conventional analgesic regimens and where increased uptake in the painful lesions is demonstrated on bone scan

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment

1. Strontium-89 plus cisplatin
2. Strontium-89 alone
3. Radiotherapy
4. Strontium-88
5. Rhenium-186
6. Hemibody radiotherapy
7. Samarium-153
8. Tin-117m
9. Phosphorus-32

MAJOR OUTCOMES CONSIDERED

- Pain response
- Analgesic consumption
- Overall survival
- Adverse effects
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The MEDLINE (1966 through January 2004), EMBASE (1980 to 2004 week 10), CANCERLIT (1975 through October 2002), and Cochrane Library (2003, Issue 4) databases were searched. "Radioisotopes" (Medical Subject Heading [MeSH] and text word), "Radiopharmaceuticals" (MeSH and text word), "Strontium Radioisotopes" (MeSH and text word), "Samarium" (MeSH and text word), "rhenium" (text word) and "tin" (text word) were combined with "Bone

Neoplasms" (MeSH and text word) and "Pain" (MeSH and text word). In addition, conference proceedings of the annual meetings of the Society of Nuclear Medicine (1997 to 2003), the American Society of Clinical Oncology (1995 to 2003), the European Association of Nuclear Medicine (2002), and the American Society for Therapeutic Radiology and Oncology (2000 to 2003) were searched for abstracts of relevant trials. Relevant articles and abstracts were selected and reviewed by one reviewer, and the reference lists from these sources were searched for additional trials, as were the reference lists from the relevant review articles. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guidelines Clearinghouse (<http://www.guideline.gov/>) were searched for existing evidence-based practice guidelines.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were:

1. Randomized controlled trials or meta-analyses of randomized controlled trials that compared radiopharmaceuticals to placebo, another radiopharmaceutical, or another active treatment in patients with bone pain due to metastatic disease
2. Randomized phase II trials including radiopharmaceutical treatment as one of the trial arms
3. Phase I and II trials investigating radiopharmaceuticals for the treatment of painful bone metastases
4. Evidence-based clinical practice guidelines and systematic reviews on the use of radiopharmaceuticals in patients with painful bone metastases

Trials had to report on at least one of the following outcomes to be considered in the systematic review of the evidence: evaluation of pain, analgesic consumption, quality of life, adverse effects, or overall survival.

Exclusion Criteria

1. Trials including fewer than 20 patients were excluded from the review.
2. Trials published in a language other than English were excluded, due to limited resources being available for translation.

NUMBER OF SOURCE DOCUMENTS

Six randomized controlled trials, one randomized phase II trial, one randomized crossover trial and 27 single-arm phase II trials, phase I trials, or retrospective case series investigated strontium-89 (Sr-89) and met the eligibility criteria for this systematic review. Three randomized controlled trials, two randomized phase II trials, and six single-arm phase II and phase I trials were located that investigated the use of samarium-153 (Sm-153). One randomized controlled trial, two randomized phase II trials, one randomized crossover trial, and 13 single-arm phase II and phase I trials were located that investigated the use of rhenium-186 (Re-186) or rhenium-188 (Re-188). One phase I dose-escalation trial of tin-117m (Sn-117m) and one single-arm phase II trial of phosphorus-32 (P-32) were located. A summary of the primary evidence included in this practice guideline report is provided in Table 1 in the original guideline document.

In addition to the primary studies of the various radiopharmaceuticals, one evidence-based practice guideline, one systematic review, and three economic analyses were located.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The available randomized controlled trials investigating the use of radiopharmaceuticals for the palliation of metastatic bone pain were quite heterogeneous with respect to the radiopharmaceutical used, the dosage and the comparison arm. Therefore, pooling of the data was judged to be inappropriate.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

A subcommittee of the Therapeutic Radiopharmaceutical Guidelines Group set the original search strategy and reviewed the available literature for inclusion in this guideline report. The working group decided to restrict the review of the literature to randomized phase III trials and larger, prospective phase I and II trials where pain response using an objective response scale was reported. The results of the literature search were discussed at a meeting with the entire group in November 2002. It was decided that pooling of the pain response data was not appropriate, given the heterogeneity in response scales used, disease histologies treated, radiopharmaceuticals and doses used, and comparisons made. The group agreed, however, that sufficient evidence existed on which to base recommendations around the use of radiopharmaceuticals as a palliative intervention for uncomplicated bone pain from metastatic cancer. It was acknowledged that the combination of radiopharmaceuticals with other modalities such as chemotherapy or radiotherapy may carry benefits in terms of more durable pain response or delay in the time to new symptomatic bone metastases but that there was insufficient evidence to make recommendations for radiopharmaceutical use in this setting. The group concluded that further research into the combination of radiopharmaceuticals with other agents, as well as the appropriate time to introduce radiopharmaceuticals (for symptomatic control or as an adjunct to reduce the incidence of new painful bone metastases) was required. It was also

emphasized that appropriate patient selection (good performance status, adequate bone marrow reserve, reasonable short-term life expectancy) was essential to the optimal use of radiopharmaceuticals.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

One study reported a retrospective evaluation of cost of care for patients on the trial of local field radiotherapy with or without adjuvant strontium-89 (Sr-89). The addition of Sr-89 to local field radiotherapy was associated with cost savings over radiotherapy alone. The authors estimated the savings as sufficient to offset the costs of the Sr-89 therapy and concluded that Sr-89 plus local field radiotherapy was a potentially cost-effective therapy.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 216 practitioners in Ontario (45 medical oncologists, 82 nuclear medicine physicians, and 89 radiation oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on November 6, 2003. Follow-up reminders were sent at two weeks (post card), four weeks (complete package mailed again), and two months (complete package mailed again). The Therapeutic Radiopharmaceutical Guidelines Group reviewed the results of the survey.

Final approval of the guideline report was obtained from the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Use of radiopharmaceuticals (strontium-89 and samarium-153) may be considered as an option for the palliation of multiple sites of bone pain from metastatic prostate cancer as these patients represented the majority (80%) of patients experiencing benefit in clinical trials where histology was specified.
- Use of radiopharmaceuticals (strontium-89 and samarium-153) may also be considered for patients with lung and breast cancers. These patients represented a substantial minority (20%) in the clinical trials where histology was specified.

- The selection of patients for radiopharmaceutical therapy should consider the patient's marrow function, performance status, recent use of other marrow suppression agents (chemotherapy or radiotherapy), unsuitability for alternate palliative interventions (wide field or local field radiotherapy, hormone therapy, chemotherapy, bisphosphonates), and anticipated life expectancy.
- Ideally the decision for radiopharmaceutical use should be based on a multidisciplinary (radiation oncology, nuclear medicine, medical oncology, palliative care) patient assessment.
- Patients with a partial response or complete response following radiopharmaceutical therapy may be considered for repeat administration for persistent or recurrent bone pain if the following is ruled out: rapid systemic disease progression, mechanical component to bone pain, underlying other bone pathology, impending or established fracture, or spinal cord compression.
- The recommended dose for strontium-89 is 148 mBq (4mCi) by slow intravenous injection (1 to 2 minutes), accompanied by intravenous or oral hydration (at least 500 mL). The recommended dose for samarium-153 is 37 mBq/kg (1 mCi/kg) by slow intravenous injection (1 to 2 minutes), accompanied by intravenous or oral hydration (at least 500 mL).

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Familiarity with and effective use of radiopharmaceuticals in the palliation of metastatic bone pain

POTENTIAL HARMS

Hematologic toxicity has been the primary adverse effect associated with radiopharmaceutical administration reported in the studies that assessed this outcome. Thrombocytopenia was reported as an adverse effect in 30 to 50% of patients treated with radiopharmaceuticals and was generally mild (grade 2 or less). Neutropenia was less commonly reported as a side effect when radiopharmaceuticals were used alone but was more common in reports of radiopharmaceuticals combined with chemotherapy. In studies comparing radiopharmaceuticals to radiotherapy, the incidence of nausea and vomiting was substantially less ($\leq 10\%$) with radiopharmaceutical treatment than with local (27%) or hemibody (43%) radiation. However, it should be noted that the

availability of newer, more effective antiemetics such as 5-HT₃ antagonists may reduce the advantages of radiopharmaceuticals over radiotherapy in this regard.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Patients with painful bone metastases should have appropriate analgesic and supportive care measures instituted in addition to other palliative interventions such as radiopharmaceuticals.
- Patients with more limited painful bone involvement, or painful lesions confined to one side of the diaphragm should be considered for focal or wide field (hemibody) external beam radiotherapy. Information on histologic subtype was not available for a significant proportion (30–40%) of patients treated on trials of palliative radiopharmaceuticals.
- The cost benefit of single-agent radiopharmaceuticals relative to other systemic agents such as bisphosphonates and chemotherapy remains to be determined.
- A subset of trials has suggested an increased benefit in terms of pain palliation with the combination of a radiopharmaceutical agent with external beam radiotherapy or chemotherapy. The combination of radiopharmaceuticals with these modalities or with others such as bisphosphonates requires further investigation in clinical trials.
- The administration of radiopharmaceuticals should be restricted to those patients with adequate bone marrow reserve and performance status (Karnofsky Performance Status >60), anticipated life expectancy of greater than four months, and uncomplicated bone metastases (no pathologic fracture or impending pathologic fracture, no spinal cord compression, or no hypercalcemia).
- The use of newer radiopharmaceuticals such as rhenium and radioactive tin are under investigation for the palliation of metastatic bone pain but are not approved for use outside clinical trials in Canada.
- Samarium-153 is currently licensed in Canada, but there is no distributor at this time.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Therapeutic Radiopharmaceutical Guidelines Group. Radiopharmaceuticals for the palliation of painful bone metastases [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Jun 15. 36 p. (Practice guideline report; no. 14-1). [74 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Jun 15

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Therapeutic Radiopharmaceuticals Guidelines Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Therapeutic Radiopharmaceutical Guidelines Group disclosed potential conflict of interest information. No conflicts were declared.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Radiopharmaceuticals for the palliation of painful bone metastases. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2004 Jun 15. Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).
- Browman GP, Levine MN, Mohide EA, Hayward RS, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995; 13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on September 24, 2004. The information was verified by the guideline developer on October 20, 2004.

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The logo for FIRSTGOV, with "FIRST" in blue and "GOV" in red, separated by a small red star.

